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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,786	11/08/2000	Sudhir Agrawal	47508.700	2469

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/708,786	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-15,17-24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-15, 17-24, 26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to Applicants Amendment filed August 13, 2003.

Claims 7, 16, and 25 have been canceled. Claims 1, 6, 8, 9, 10, 15, 19, 24 and 26 have been amended.

Claims 1-6, 8-15, 17-24, 26 and 27 are pending in the instant application.

Applicant's amendment to Figure 6 to distinguish between treatment regimens in the figure's legend is acknowledged.

The new Oath/Declaration to correct for non-initialed and/or non-dated alterations is acknowledged.

The specific reference to priority in the first line of the Specification is acknowledged.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 19-27 were rejected under 35 USC, 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is withdrawn in view of Applicants arguments, filed August 13, 2003.

Claims 1-6, 8-15, 17-24, 26 and 27 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is withdrawn in view of Applicants arguments, filed August 13, 2003.

Claims 1-6, 8-15, 17-24, 26 and 27 were rejected under 35 USC, 112 first paragraph, because the specification while being enabled for a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising co-administering an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1, does not reasonably provide enablement for a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, provided that the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1. This rejection is maintained for the reasons of record set forth in the previous Office Action, filed March 11, 2003.

Applicants argue that further explicit disclosure of methods of making specific oligonucleotides not having the sequence corresponding to SEQ ID NO:1 for use in the claimed invention, beyond the teachings of the instant application, are not needed to support enablement, because such oligonucleotides not having the sequence corresponding to SEQ ID NO:1 are well known in the art and would not require undue experimentation to make and use.

This is not found persuasive because the Specification is not enabling for any/all oligonucleotides. The issue is would any/all oligonucleotides have the biological activity to function to statistically significantly potentiate the activity of a prodrug? Applicants have not described which oligonucleotides, excluding SEQ ID NO:1 or SEQ ID NO:2, will exhibit the specific functional language of the claims (e.g. the requirement for statistically significantly potentiate the activity of a prodrug). The specification does not teach an oligonucleotide that does not have the sequence of SEQ ID NO:1 or SEQ ID NO:2 that would retain the function to statistically significantly potentiate the activity of a prodrug. Further, Agrawal et al. (International Journal of Oncology, 2001 Vol. 18:1061-1069) teach "the potentiation of antitumor activity of irinotecan is dependent on the dose of irinotecan and chemically modified oligonucleotide, suggesting requirement of the presence of a certain level of irinotecan and oligonucleotide in the system" (see page 1067, last paragraph and page 1068, first column). This statement indicates that specific oligonucleotides will act to potentiate prodrug acitivity while others will not. Thus, undue experimentation would be required of the skilled artisan to determine which oligonucletides will meet the functional limitations of the claims.

Applicants argue that in order to expedite prosecution, Applicants have amended the independent claims to specify "an oligonucleotide" rather than a "polyanion". Applicants contend that this amendment, in addition to the state of the art of oligonucleotide production, and the broad teachings of the specification, supports the enablement requirement of the claimed invention.

Applicants arguments have been considered but are not found persuasive because, as stated above, Applicants have not described which oligonucleotides will exhibit the specific

functional language of the claims. Applicant has provided little or no guidance beyond the mere presentation of two sequences, one of which is excluded in the claims, to enable one of ordinary skill in the art to determine, without undue experimentation, those oligonucleotides which statistically significantly potentiate the activity of a prodrug. Additionally, such a broad definition might also read on previously characterized oligonucleotides, or alternatively, might include oligonucleotides with additional functions or activities neither envisioned nor enabled by applicants in the current invention. Therefore, undue experimentation would be required of the skilled artisan to determine those oligonucleotides which meet the functional limitations of the claimed invention.

Claim Rejections - 35 USC § 102

Claims 10, 14, 15, 17 and 18 were rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al [US Patent No. 6,013,786]. This rejection is withdrawn in view of Applicants arguments that campothecin (CPT) is not a prodrug, filed August 13, 2003.

Claim Rejections - 35 USC § 103

Claims 1-6, 8-15, 17-24, 26 and 27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Totora et al., (Proceedings of the National Academy of Sciences, 1997, 94:12586-91), Wang et al., Chen et al. [U.S. Patent 6013786] and Baracchini et al. [U.S. Patent No. 5,801,154]. This rejection is maintained for the reasons of record set forth in the previous Office Action, filed March 11, 2003.

Applicants argue that Chen et al [US Patent No. 6,013,786] fail to teach the use of a prodrug and therefore the cited references fail to render obvious the claimed invention because

they fail to teach or suggest the use of a prodrug. Applicants further argue that the previous Office Action fails to provide a prima facie case for obviousness of the claimed invention because it does not provide a reference utilizing a prodrug.

Applicants arguments have been fully considered but are not found persuasive because while Chen et al. do not teach the use of a prodrug, Totora et al. and Wang et al. cure the deficiencies of Chen et al. Chen et al. was relied upon to show the mdm-2 oncogene as a novel target for human cancer therapy using a polyanion (oligonucleotide phosphorothioate) approach. Totora et al. teach the synergistic inhibition of human cancer cell growth by cytotoxic drugs, including prodrugs, and a phosphorothioate antisense oligonucleotide. In this instance the prodrug taught by Tortora et al. is docetaxel (see page 12488, last paragraph and page 12489, first column). Tortora et al. further teach a method to study whether any cooperative effect may occur between the phosphorothioate antisense oligonucleotide and a series of cytotoxic drugs, including prodrugs, acting by different mechanisms (see page 12591 last paragraph).

Wang et al. have taught an mdm-2 oncogene as a novel target for human cancer therapy using a polyanion (oligonucleotide phosphorothioate) approach. Wang et al. further teach that following administration of an anti-MDM2 phosphorothioate antisense oligonucleotide, *in vivo* antitumor activity was observed in nude mice. Wang et al. assert the future development of anti-MDM2 antisense oligonucleotide phosphorothioate as a cancer therapeutic agent used alone or in combination with conventional chemotherapeutics.

As stated in the previous Office Action, one of ordinary skill in the art would have been motivated to potentiate the activity of a cytotoxic prodrug, such as CPT-11, with phosphorothioate oligonucleotides since Tortora et al. teach synergistic inhibition of human

cancer cell growth by cytotoxic drugs, including prodrugs, and phosphorothioate antisense oligonucleotides. One of ordinary skill in the art would have been motivated to co-administer a prodrug with an mdm-2 antisense oligonucleotide, for example, in a manner that potentiates the activity of the prodrug because Wang et al. and Chen et al. have taught an mdm-2 oncogene as a novel target for human cancer therapy using an oligonucleotide approach and Tortora et al. taught the synergistic inhibition of cancer growth by the co-administration of a prodrug and a phosphorothioate antisense oligonucleotide. One of ordinary skill in the art would have been motivated to modify the phosphorothioate oligonucleotide to include oligonucleotide phosphorothioate oligonucleotides with 2'-O-methylribonucleoside modifications at varying positions and had a reasonable expectation of success since the art taught the use of modified phosphorothioate oligonucleotides as particularly useful therapeutics for oral administration (Baracchini et al.).

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
October 29, 2003

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER